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A Risk Score to Estimate the Likelihood of Coronary Artery Bypass Surgery During the Index Hospitalization Among Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

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OBJECTIVES A simple risk score on admission to estimate the likelihood of in-hospital coronary artery bypass graft surgery (CABG) might be useful in selecting patients for early clopidogrel therapy.

BACKGROUND Routine early use of clopidogrel in patients with unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) is associated with increased risk of bleeding in patients who undergo early CABG.

METHODS The test cohort utilized to derive the score was the 2,220 patients with UA/NSTEMI enrolled in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction-18 (TACTICS–TIMI-18) trial. Patients who underwent CABG after randomization during index hospitalization were identified and were compared with patients who did not undergo in-hospital CABG.

RESULTS Overall, 362 patients (16.3%) underwent CABG during the index hospitalization. Patients with a history of prior CABG (n = 484) were significantly less likely to undergo in-hospital CABG (odds ratio [OR], 0.34). Five additional variables independently associated with CABG were identified: elevated troponin (OR, 3.9), prior stable angina (OR, 1.8), ST-segment deviation ≥0.5 mm (OR, 1.7), male gender (OR, 1.6), and history of peripheral arterial disease (OR, 1.6). A CABG risk score was generated by assigning numerical values to each of the variables based upon these odds ratios. Coronary artery bypass surgery rates increased significantly with increasing risk scores (6.2% for a risk score <3.0, 21.9% for 3 to 5, and 54.6% for >5.0). The association of the risk score with CABG was highly significant ($p < 0.0001$, c-statistic 0.72). The association remained significant in the validation cohorts from TIMI-11B trial and TIMI-III registry.

CONCLUSIONS Among patients with UA/NSTEMI, a novel risk score based on admission clinical variables can be used to estimate the likelihood of CABG. These data may assist in the identification of patients who might derive optimal benefit from early initiation of clopidogrel therapy. (J Am Coll Cardiol 2004;44:799–803) © 2004 by the American College of Cardiology Foundation

Combination anti-platelet therapy with aspirin and clopidogrel improves outcomes in patients with unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) (1). The current American College of Cardiology/American Heart Association guidelines recommend addition of clopidogrel to aspirin in patients with UA/NSTEMI upon admission to the hospital (2). These beneficial effects are mediated by the enhanced platelet inhibition that follows administration of combination therapy, which also results in an increase in the risk of major bleeding in patients undergoing early coronary artery bypass graft surgery (CABG) within five days of administration of clopidogrel (1,3,4). Data from several recent trials of UA/NSTEMI indicate that 8% to 25% of patients undergo CABG after coronary angiography (1,5–7). Withholding clopidogrel for at least five days before CABG reduces the risk of perioperative bleeding (1), but may lead to prolonged hospitalization. Further, a policy of withholding clopidogrel until cardiac catheterization may reduce any benefit of pretreatment with clopidogrel in the reduction of adverse cardiac outcomes in the 50% to 60% of UA/NSTEMI patients who undergo percutaneous coronary intervention (PCI) (8). An ideal strategy would be to pretreat patients who will require PCI or continued medical therapy, and withhold clopidogrel in patients with high likelihood of requiring early CABG. Thus, in patients with UA/NSTEMI, ability to estimate the likelihood of in-

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Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
IQ_	= inter-quartile
NSTEMI	= non–ST-segment elevation myocardial infarction
OR	= odds ratio
PAD	= peripheral arterial disease
PCI	= percutaneous coronary intervention
TACTICS–TIMI-18	= Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction-18
UA	= unstable angina

hospital CABG upon admission using clinical parameters that are readily available on presentation may be useful. The main objective of this study was to develop and test a simple clinical risk score based on admission clinical variables to estimate the likelihood of in-hospital CABG in patients with UA/NSTEMI.

METHODS

The study population for design of the CABG risk score was derived from TACTICS TIMI 18 trial. The details of Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction-18 (TACTICS–TIMI-18) trial have been previously published (7). A total of 2,220 patients with UA/NSTEMI were randomly assigned to an early invasive strategy that included routine cardiac catheterization within 4 to 48 h and revascularization as appropriate, or to a conservative strategy in which cardiac catheterization was performed only if the patient had objective evidence of recurrent ischemia or an abnormal stress test. All patients received aspirin, heparin, and tirofiban. The primary end point was a composite of death, non-fatal reinfarction, and rehospitalization for acute coronary syndromes at six months. For the purpose of this study, patients from the total TACTICS–TIMI-18 population who underwent CABG after randomization during index hospitalization were identified and were compared with patients who did not undergo in-hospital CABG.

Statistical analysis. Clinical characteristics of patients who underwent CABG during the index hospitalization were compared with patients who did not undergo CABG. Initial univariate comparisons of the baseline clinical variables were performed. Variables that achieved a significance level of $p < 0.20$ were then selected for testing in a multivariate backward step-wise logistic regression model. A p value of <0.05 was required for retention in the final model. A CABG risk score was generated by assigning numerical values for each variable independently associated with CABG. A negative value was assigned if the variable was significantly associated with reduced likelihood of CABG. The final score was constructed by simple arithmetic sum of numerical values assigned to each of the variables present. Risk score categories were collapsed (e.g., −2, −1, and 0) when the prevalence of a given score was <1%. The c-statistic, or area under the receiver operator characteristic curve, was used to assess the discriminatory capacity of the risk score. Test for trend across ordered groups was performed for the risk score groups (Stata version 7.0, Stata Corp., College Station, Texas).

Validation of the risk score. The risk score was validated in two separate cohorts of patients with UA/NSTEMI enrolled in the TIMI-11B trial and TIMI-III registry, using the risk score model in the TACTICS–TIMI-18 trial. The design and results of TIMI-11B trial and TIMI-III registry have been reported (9–11). The TIMI-11B trial evaluated 3,910 patients with UA/NSTEMI randomly assigned to either unfractionated heparin or enoxaparin. Further in-hospital management of the patients, including decisions on revascularization, was left to the discretion of the treating physician (10). The TIMI-III registry was a prospective, observational study of a wide variety of patients with UA/NSTEMI correlating clinical characteristics to outcomes. A total of 3,318 patients were prospectively followed for one year; TIMI-III registry did not mandate strict inclusion or exclusion criteria other than admission diagnosis of UA/NSTEMI. In addition, the management of patients was left to the discretion of the treating physician. Thus, the study provided an insight into the "real world" management of patients with UA/NSTEMI (11). In each of these validation cohorts, the ability of the risk score to estimate the need for CABG was evaluated.

RESULTS

Data from 2,220 patients with UA/NSTEMI in the TACTICS–TIMI-18 trial were utilized as the derivation cohort. Of these, 362 patients (16.3%) underwent CABG during the index hospitalization. Overall, 22% of the patients randomized to the invasive arm and 15% of the patients randomized to the conservative arm underwent in-hospital CABG. The median time from randomization to in-hospital CABG in the overall TACTICS–TIMI-18 population was 3.8 days (inter-quartile [IQ] range 2.5, 6.0). In the invasive arm, it was 3.4 days (IQ range 1.9, 4.9), and in the conservative arm it was 5 days (IQ range 3.7, 7.9).

The baseline clinical characteristics of the two populations are shown in Table 1. Patients who underwent CABG were more likely to be male and were older. They were significantly less likely to have had prior PCI or CABG. They had a higher prevalence of diabetes mellitus, history of prior angina, prior MI, and a history of peripheral arterial disease (PAD). They were also more likely to have ST-segment deviation (ST-segment elevation or depression ≥0.5 mm) on their admission electrocardiogram as well as elevated troponin.

Table 1. Comparison of Baseline Clinical Characteristics Screened as Candidate Variables for the Design of the CABG Risk-Score in TACTICS–TIMI-18 Trial

Characteristics	No CABG (n = 1857)	CABG (n = 362)	p Value
Mean age (yrs)	61 ± 12	63 ± 10	0.004
Males (%)	64	74	0.001
Caucasian (%)	77	80	0.3
Hypertension (%)	66	67	0.6
DM (%)	27	33	0.02
Hyperlipidemia (%)	60	63	0.3
Current smoker (%)	28	27	0.7
Family history of CAD (%)	44	41	0.3
Prior MI (%)	40	32	0.004
Prior PTCA (%)	29	19	0.0001
Prior CABG (%)	24	10	0.0001
History of angina (%)	12	17	0.02
CHF (%)	7	7	0.9
Prior aspirin (%)	66	67	0.9
History of CVA (%)	5.8	4.4	0.3
History of PAD (%)	7.1	10.0	0.08
ST-segment deviation ≥ 0.5 mm	36	52	<0.0001
Positive troponin (%)	55	84	<0.0001

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; DM = diabetes mellitus; MI = myocardial infarction; PAD = peripheral arterial disease; PTCA = percutaneous transluminal coronary angioplasty.

Of the variables evaluated, six remained statistically significant in the multivariate analysis. Patients with history of prior CABG (n = 484) were significantly less likely to undergo repeat CABG (odds ratio [OR] 0.35, $p < 0.0001$), and only 7.4% of these patients eventually underwent repeat CABG. The other variables independently associated with in-hospital CABG (Table 2) were elevated troponin (OR 3.9, $p < 0.0001$), history of prior angina (OR 1.8, $p = 0.001$), ST-segment deviation on the initial electrocardiogram (OR 1.7, $p < 0.0001$), history of PAD (OR 1.6, $p = 0.038$), and male gender (OR 1.6, $p = 0.001$) (c-statistic 0.72 for the full model, $p < 0.0001$). Because an elevated troponin was most strongly associated with the need for CABG, a score of 3 was assigned for this variable. A score of −2 was assigned for history of prior CABG. The other four variables were each assigned a score of 1. The overall CABG risk score was calculated by the arithmetic sum of individual scores in the test cohort.

Table 2. Variables Independently Associated With CABG in Multivariate Analysis

Variables	Odds Ratio	95% CI	p Value	Risk Score
History of CABG	0.35	0.2–0.5	<0.0001	−2
(+) Troponin	3.9	2.7–5.5	<0.0001	3
Prior angina	1.8	1.3–2.6	0.001	1
ST-segment deviation ≥ 0.5 mm	1.7	1.3–2.2	<0.0001	1
History of PAD	1.6	1.1–2.6	0.038	1
Male gender	1.6	1.2–2.2	0.001	1

CABG = coronary artery bypass graft surgery; CI = confidence interval; PAD = peripheral arterial disease.

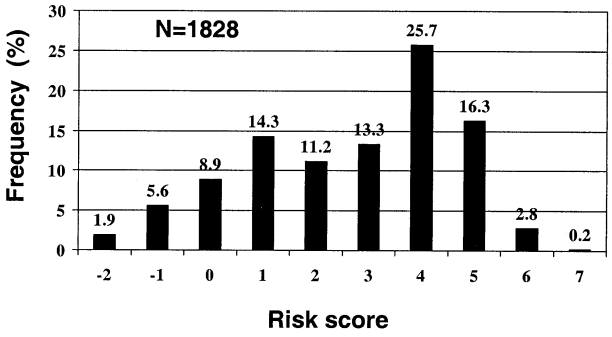

Figure 1. Distribution of the coronary artery bypass surgery risk score in the overall TACTICS–TIMI-18 patient population. Risk score: <3.0, 42%; 3 to 5, 55%; >5.0, 3%.

The distribution of the CABG risk scores in the TACTICS–TIMI-18 population is shown in Figure 1. Altogether, 42% of patients had a low risk score of <3.0, 55% had intermediate risk scores of 3 to 5, and 3% of patients had a high risk score >5.0.

The association of CABG with increasing risk scores in the overall TACTICS–TIMI-18 population is shown in Figure 2. There was a significant increase in the rates of CABG with increasing risk scores. Only 6.2% of patients with a low risk score <3.0 and 21.9% with intermediate risk scores of 3 to 5 underwent CABG compared with the significantly greater 54.6% of patients with a high risk score >5.0 ($p < 0.001$). Similar association of CABG with increasing risk scores was observed in both the invasive and conservative arms (Fig. 3). The sensitivity, specificity, positive predictive value, and negative predictive value for high risk scores versus low and intermediate risk scores were 55%, 85%, 10%, and 98.4%, respectively. Importantly, the association of the risk score with rates of PCI was not as significant as that of CABG. The rates of PCI seemed to be more evenly distributed; 25.2%, 39.7%, and 25.5% in patients with low, intermediate, and high risk scores, respectively.

Validation of risk score. Validation of the CABG risk score in the TIMI-11B trial and TIMI-III registry are shown in Figures 4 and 5. Overall, the number of patients who underwent CABG was much lower in the TIMI-11B

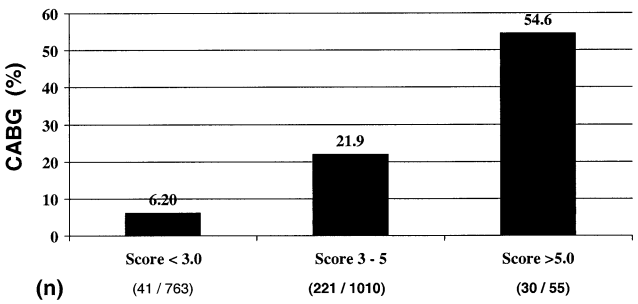

Figure 2. Rates of in-hospital coronary artery bypass surgery (CABG) in patients with prior CABG and low, intermediate, and high CABG risk scores in the overall TACTICS–TIMI-18 population (n = 1,828). Association of the risk score with in-hospital CABG, p value for trend <0.0001; c-statistic 0.72.

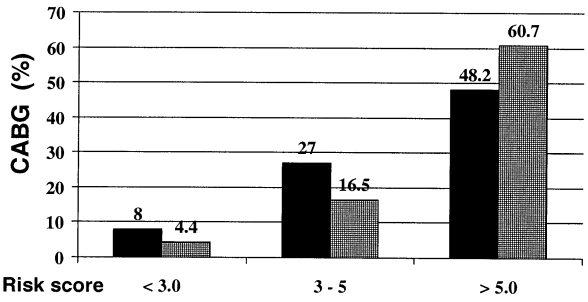

Figure 3. Association of the risk score with in-hospital coronary artery bypass surgery (CABG) in the invasive and conservative arms of TACTICS–TIMI-18 trial. **Solid bars** = invasive; **hatched bars** = conservative. Invasive arm (n = 921) p value for trend <0.0001, c-statistic 0.71; conservative arm (n = 907) p value for trend <0.0001, c-statistic 0.73.

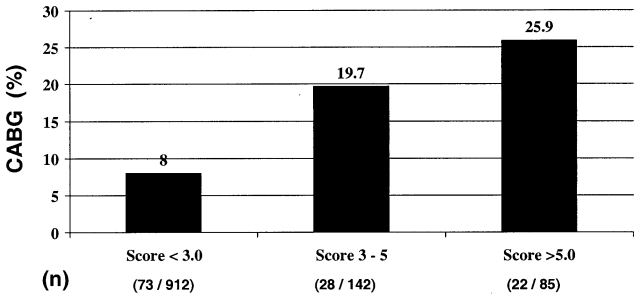

Figure 5. Validation of the coronary artery bypass surgery (CABG) risk score in Thrombolysis In Myocardial Infarction (TIMI)-III registry patient population with unstable angina and non–ST-segment elevation myocardial infarction. Association of the risk score with in-hospital CABG in TIMI-III registry (n = 1,139), p value for trend <0.0001; c-statistic 0.66.

trial than in the TACTICS–TIMI-18 trial (6.5% vs. 16.3%). However, despite the low rates of CABG, there was a similar significant association between increasing risk scores and the need for CABG at eight days (Fig. 4). Rates of CABG were 4.5% and 7.7% in patients with low and intermediate risk scores, respectively, compared with 11.5% in patients with high risk scores (c-statistic 0.61, $p < 0.0001$). Only 1,139 patients from TIMI-III registry qualified for this analysis, as the information on variables from the model was not routinely available and elevated creatine kinase MB was substituted for elevated troponin in the risk score. Nonetheless, the CABG rates increased significantly from 8% in patients with low risk scores <3.0, to 20% in patients with intermediate risk scores of 3 to 5, and 26% in patients with high risk scores >5.0 ($p < 0.0001$; c-statistic 0.66) (Fig. 5).

DISCUSSION

These results indicate that, using readily available admission clinical variables, a simple risk score can be constructed to estimate the likelihood of CABG in a patient presenting with UA/NSTEMI. A CABG risk score of >5.0 was associated with high likelihood of CABG (55%) during index hospitalization. The association of the risk score with CABG was validated in two independent UA/NSTEMI patient populations.

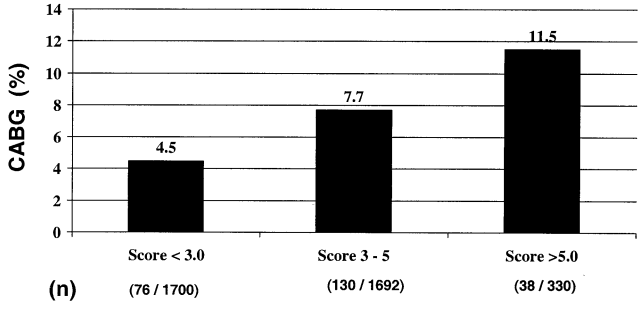

Figure 4. Validation of the coronary artery bypass surgery (CABG) risk score in Thrombolysis In Myocardial Infarction (TIMI)-11b patient population with unstable angina and non–ST-segment elevation myocardial infarction. Association of the risk score with in-hospital CABG in TIMI-11b (n = 3,722), p value for trend <0.0001; c-statistic 0.61.

In patients with UA/NSTEMI, the beneficial effects of early combination therapy with aspirin and clopidogrel has clearly been demonstrated at 30 days and 1 year, and were apparent within the first 24 h after a loading dose of clopidogrel (1). However, the irreversible platelet inhibition that follows this combination therapy has been associated with increased risk of perioperative major bleeding among patients undergoing early CABG. Withholding clopidogrel for at least five days (i.e., duration of effect of clopidogrel) before CABG reduces the risk of perioperative bleeding. However, such a strategy may lead to adverse events and prolonged hospitalization due to the five to seven days waiting period before CABG. These factors have contributed to the considerable variation in the early use of clopidogrel in patients with UA/NSTEMI (12,13). The ability to estimate the likelihood of CABG upon admission, using readily available clinical parameters, may help aid in defining the optimal timing of clopidogrel administration. The results of this study suggest that a prior history of CABG or, overall, a CABG risk score <3.0 (42% of patient population in TACTICS–TIMI-18 trial) can help identify patients at low risk of requiring early CABG, in whom clopidogrel may be safely administered on admission.

Due to risks associated with repeat CABG, most patients with prior CABG are likely to be treated with PCI or medical therapy unless they have universally failed grafts. Our data bore this out; patients with prior CABG were 65% less likely to undergo repeat CABG. Only 7.4% of these patients underwent repeat CABG. Given the strong negative association, these patients are, as a group, at reduced risk for repeat CABG, and, hence, in these patients there is less reason to consider delaying the administration of clopidogrel.

A CABG risk score >5.0 is associated with a high likelihood of requiring in-hospital CABG. Only 3% of patients with UA/NSTEMI in TACTICS–TIMI-18 trial had a CABG risk score >5.0, yet a dramatic 55% of these patients underwent CABG, compared with 6.2% and 21.9% in patients with low and intermediate risk scores, respec-

tively. The specificity and the negative predictive value of the risk score were high, 85% and 98.4%. Thus, in patients with UA/NSTEMI, a low CABG risk score <3.0 is associated with low likelihood of CABG, and clopidogrel can be initiated immediately on admission. On the other hand, a high CABG risk score >5.0 is strongly associated with need for CABG, and one might consider withholding clopidogrel until early angiography and definition of coronary anatomy. However, the assumption that such a strategy of withholding clopidogrel until early angiogram improves safety with similar efficacy is speculative and needs to be tested prospectively in future clinical trials. Patients with intermediate risk scores of 3 to 5 constituted 55% of TACTICS–TIMI-18 population and had a CABG rate of 21.9%. Although the decision on clopidogrel in these patients could be challenging, it should be individualized using judgment on risk versus benefit. It is likely that, with the advent of drug-eluting stents, an increasing proportion of these patients may be treated with multivessel PCI instead of CABG.

Conclusions. In patients with UA/NSTEMI, a simple risk score based on admission clinical variables estimates the likelihood of CABG. A risk score of <3.0 is associated with a very low likelihood of CABG, and a risk score of >5.0 is associated with a high likelihood of CABG during hospitalization. These data may help decisions on initiation of clopidogrel upon admission with UA/NSTEMI.

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